Journal of the Washington Academy of Sciences,
Volume 78, Number 1, Pages 38–46, March 1988

Angiostrongyliasis Cantonensis (Eosinophilic Meningitis): Historical Events in its Recognition as a New Parasitic Disease of Man

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ABSTRACT

In April 1961 the rat lungworm, *Angiostrongylus cantonensis* was the principal suspect as the etiological agent of the eosinophilic meningitis epidemics of 1948–1957 in the Pacific.[2,4–6] This was affirmed by: (a) presence of rat infection in all areas where the disease occurred;[4,7,8] (b) human infection resulting from ingesting raw slugs[4,29] and freshwater prawns;[12] (c) experimental infection of simian primates;[4,14] and (d) recovery of the parasite in human cases.[32,39,45,47,51] These epidemics appear related to the spread of the giant African snail, *Achatina fulica,* believed responsible for introducing the parasite to the Pacific area.[10]

Introduction

In the background leading to the recognition of angiostrongyliasis cantonensis as a new parasitic disease of man, was the occurrence of three epidemics of eosinophilic meningitis of unknown etiology in Micronesia, New Caledonia and Tahiti from about 1948 to 1957. Rosen and associates in searching for the etiological agent, theorized that the disease was caused by a worm parasite in the skipjack tuna or related fish eaten raw.[44] On the other hand, Alicata in April, 1961,[2,4–6] strongly suspected that the rat lungworm, *Angiostrongylus cantonensis* (Fig. 1), served as the etiological agent. This new theory was soon confirmed by the independent observations of previous and subsequent investigators reported herein. Their findings led to recognition of a new parasitic disease of man, referred to as angiostrongyliasis cantonensis[27] and Alicata's Disease.[31]

The purpose of this paper is to summarize the more important events that led to the identification of the cause and means of transmission of this new disease,

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Fig. 1. *Angiostrongylus cantonensis*: adult male and female. ×1.3 (Alicata and Jindrak, 1970)

and to reflect as to why, previously unknown in the Pacific, its appearance occurred in this area about the middle of this century.

Important Historical Dates and Events

1933

Chen in 1933 observed lungworm nematodes among rats in Canton, China,[24] and in 1935 described them under the name of *Pulmonema cantonensis*.[25] Matsumoto in 1937 found similar parasites in Taiwan;[37] in the same year, Yokogawa described them as *Haemostrongylus ratti*.[52] Later the parasite was established taxonomically by Dougherty in 1946 as *Angiostrongylus cantonensis*.[26]

1945

Nomura and Lin, 1945, were first to observe the presence of young adult nematodes *A. cantonensis* (but referred to as *H. ratti*) in the cerebrospinal fluid that they had casually recovered from a patient with symptoms of meningitis.[39] Although they did not definitely associate this parasite with the disease, nor make further investigations, they suspected that food eaten raw by the patient before the illness might have been contaminated by rats. The report of these authors was published in Japanese in a local medical journal but failed to appear in abstracting journals. The reference was later cited in English by Hsieh in 1959,[30] though this also remained unknown generally until 1964, when most of the original report by Nomura and Lin was translated into English.[19] This translation, however, appeared after Alicata had already incriminated *A. cantonensis* as the cause of the eosinophilic meningitis epidemic in Tahiti.[2,6]

1948

In 1948, Bailey and two other officers of the Naval Medical Institute, Bethesda, Maryland, were assigned to investigate a supposed epidemic of encephalitis caused by a viral agent among natives of the island of Ponape, Micronesia.[18] In their original serological investigation of the disease all findings proved negative for virus, bacteria, rickettsia, leptospira, and certain protozoa and helminths. Clinically, however, they recognized that some of the patients exhibited stiffness of the neck without true rigidity, presence of skin hyperesthesia, and pleocytosis with a high percentage of eosinophils in the cerebrospinal fluid in about half of the patients examined. These findings were finally designated by them as cases of eosinophilic meningitis of a character not previously reported in the literature and of unknown etiology.

1951

Trubert in 1956 reported an epidemic in New Caledonia of a benign form of eosinophilic meningitis in more than 930 persons. This was first observed in 1951, and was of unknown etiology.[48] Clinically, it was similar to that reported earlier in Ponape.[18]

1957–1960

Franco et al. in 1960 reported cases of eosinophilic meningitis in Tahiti of unknown etiology, which they had observed since 1957.[28]

Rosen et al. similarly reported cases in Tahiti during 1958–1960.[44] In search of the etiological agent, and as result of extensive clinical and epidemiological observations, they theorized that the disease was caused by a helminth parasite of the skipjack tuna or other variety of pelagic fish commonly eaten raw in the area. Their speculation of a hypothetical parasite as the etiological agent was based on the presence of an eosinophilic syndrome, a factor often associated with an invasion of the host by helminth parasites. As far as is known, the above theory has not been confirmed.[36,50]

During 1960, Vaillant et al. from their clinical and laboratory observation of cases of fish poisoning (ciguatera) and eosinophilic meningitis in New Caledonia, postulated that a common thermostable toxin resulting from the eating of certain fish, might be involved in these maladies.[49] This theory, as yet unproved, failed to take into account the absence of eosinophilic meningitis in the Samoas and Fiji, where fish poisoning was known to occur.[34] The cases of eosinophilic meningitis that occurred in American Samoa in 1979 were believed to be caused by a recent introduction of the rat lungworm, most likely by the giant African snail, *Achatina fulica*.[20]

1961–1967

In 1961 Alicata incriminated the rat lungworm, *Angiostrongylus cantonensis*, as the cause of the eosinophilic meningitis epidemic then occurring in Tahiti.[2] This new theory, first communicated to Dr. Leon Rosen of the U.S. Public Health Service in an official letter dated April 5, 1961, stated "It is my strong suspicion that the syndrome is produced by an invasion of nematode larvae, and more specifically a species of *Angiostrongylus*," viz. *A. cantonensis*. (For full text of this letter, see Alicata and Jindrak 1970,[13] p. 6.) This letter was submitted soon after Rosen and associates had sent a manuscript for publication in which they theorized that the disease in Taihiti was caused by a helminth parasite of the skipjack tuna or other pelagic fish eaten raw in the area.[44]

The rat lungworm theory was based on a 1955 report by Mackerras and Sandars which revealed that the infective larvae of *A. cantonensis* normally and obligatorily migrated and partially developed in the brain of the rat host before migrating to the lungs, and producing an inflammatory reaction.[35] With the finding in 1960 of the rat lungworm in Hawaii[16] Alicata suspected that it might have been introduced recently in Hawaii, because in 1938 the characteristic pulmonary lesions of angiostrongylosis were not observed among rats surveyed for trichinosis in the Hawaiian Islands.[1]

Beginning in 1961, the following are the major chronological events in the search for the causative agent of eosinophilic meningitis in Tahiti, the then area of attention.

1. According to Massal[36] early in 1961, Rosen and B. J. Myers went to Tahiti to investigate a variety of marine fish ("ature", "orare", bonite et thons) in search of the hypothetical parasite suspected of being responsible for eosinophilic meningitis, but they were unsuccessful.
2. On April 5, 1961, Alicata notified Rosen of the new proposed rat lungworm theory and the need for its investigation.[2] In addition, on April 18, 1961, he made plans to travel to Tahiti that June to ascertain the presence of *A. cantonensis* in wild rats in the area.[3]
3. On May 2, 1961, Rosen[41] with the assistance of associates in Hawaii, secured the entire preserved brain of a mental patient who had died in a local hospital for diverse pathology, in-

cluding eosinophilic meningitis. A few nematodes were recovered from this brain and, on May 5, 1961, were identified by Mrs. M. B. Chitwood (personal communication) as those of *Angiostrongylus cantonensis*. It is of interest to note that even though this finding was a direct affirmation of the rat lungworm theory, Rosen doubted that *A. cantonensis* was responsible for the disease in Tahiti. As a result, he wrote an official letter dated May 18, 1961 to an associate (Dr. E. Massal) in Tahiti stating "One direct way of ruling this parasite out is to show that it does not occur in rats in Tahiti. If present however, this fact alone does not establish it as a causative agent".[6,43]

4. In June 1961, wild rats in Tahiti were found to harbor lungworms, *A. cantonensis*.[4]
5. Later in June 1961, an observation was made in Hawaii of a patient who developed achy feelings, skin hyperesthesia, and eosinophilia in the cerebrospinal fluid. This occurred ten days after the patient willfully ate two veronicellid slugs collected from an area where similar slugs were later found to be infected with third-stage larvae of *A. cantonensis*.[4,29]
6. In the autumn of 1961, late third-stage larvae of *A. cantonensis* were recovered from the brain of a young squirrel-monkey five days after experimental infection with homologous third-stage larvae.[4]
7. In February 1962, freshwater prawns in Tahiti were found to serve as paratenic (carrier) host for infective *Angiostrongylus* larvae. It was further ascertained from questioning patients that consumption of raw prawns and "taioro"—the latter a coconut sauce prepared by adding prawn juice, either of which may harbor infective *Angiostrongylus* larvae—served as an important source of human infection.[12]
8. In 1962, experiments showed that infective larvae of *A. cantonensis* produced eosinophilic meningitis in an adult monkey, *Macacus rhesus*.[14]
9. Experimental data showed that murine angiostrongylosis was present in all areas where eosinophilic meningitis had been investigated, including Hawaii and Tahiti,[4] New Caledonia,[7] Rarotonga[15] and Micronesia.[8]
10. It was theorized that the giant African snail, *Achatina fulica,* was largely responsible for the spread of the rat lungworm infection in Asia and several islands of the North Pacific.[10]

Conclusions from the above results of systematic field, laboratory, and clinical observations, plus animal experimentation, led Alicata and associates to prove the major aspects of the rat lungworm theory.[2] This theory was further substantiated by recovering at autopsy the rat lungworm from the brain of a patient who had died of eosinophilic meningitis,[45] plus similar autopsy reports from Vietnam,[32] Thailand,[47] and Taiwan.[51] As a result, all these findings assisted in confirming the etiological role of the rat lungworm, *A. cantonensis,* in cases of eosinophilic meningitis in the Pacific Basin.[31]

Discussion

One of the important features concerning eosinophilic meningitis in the Pacific was the casual concomitant finding of this disease in Taiwan with that of *A. cantonensis,*[39] a parasite which later was first theorized and subsequently proven to be the etiological agent of the disease.[2,31]

Historically, before the above findings, eosinophilic meningitis was unknown in the Pacific. As theorized by Alicata,[10] the parasite was introduced in recent times with the incoming and spread of the giant African snail, *Achatina fulica* (Fig. 2), in the southern and eastern borders of Asia and several of the northern Pacific islands (Fig. 3).

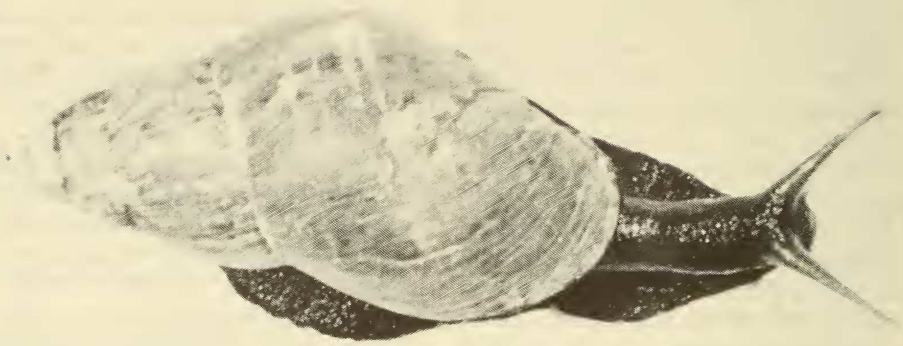

Fig. 2. The giant African snail, *Achatina fulica*. Natural size. (Alicata, 1966)

A. fulica is not only an ideal intermediate host for *A. cantonensis* but, as a scavenger, it is also able to travel extensively during wet conditions, feeding on all kinds of rotting vegetation, dead animals, and animal excreta. Mead[38] reports that man appears to have been directly or indirectly the chief dispersing agent. *A. fulica* was found in Madagascar before 1900, Ceylon in 1900, and Malaya in 1911. It was later found in eastern China about 1931, Taiwan in 1932, Okinawa in 1934, and thence was imported into Micronesia in 1938. It was found in Hawaii in 1936, and according to Beck et al. [20] in Samoa about 1975. The effects of this migration seem to demonstrate how a snail, with the help of man, enabled *A. cantonensis* to bring pestilence to a considerable portion of the North Pacific Basin.

In connection with the above distribution of the snail, angiostrongyliasis was reported in Taiwan, Guam, Hawaii, Ponape, Saipan, and Samoa 12, 25, 23, 8, 20, and 4 years, respectively after *A. fulica* was introduced to those islands. *A. cantonensis* was first observed in the rat population in China in 1933, Taiwan in 1937, Guam and Ponape in 1955, Saipan in 1963, and the Philippines in 1965.[10]

Although *A. fulica* is not known to occur in New Caledonia where angiostrongyliasis is endemic, it has been suggested that the parasite was transported there by infected mollusks or rats from Southeast Asia before World War II, possibly in connection with the importation of a large number of contract laborers for work in the nickel mines and plantations of New Caledonia.[10] From there, it is likely that the parasite was introduced by way of oceanic trade routes to Tahiti and the Cook islands. In this connection, cases of eosinophilic meningitis occurred in New Caledonia in 1951, Tahiti in 1957, and Rarotonga in 1958. Moreover, evidence indicates that before 1957, the disease was unknown in Tahiti. Since the present human infection in this area is believed to be acquired largely by consuming freshwater prawns, and since the custom of eating these crustaceans goes back many

Fig. 3. *Solid lines*: routes and approximate dates of dispersal of *Achatina fulica* from East Africa to the Pacific Islands (adopted) with revision from Mead (1961) with permission of the University of Chicago Press). *Dashed lines*: theoretical method of dispersal of the rat lungworm, *Angiostrongylus cantonensis,* from South East Asia to the islands of South Pacific and Australia. *Plain stars* show where lungworms have been found in rats. *Circled stars* show where angiostrongyliasis cantonensis has been reported. (Alicata, 1966)

generations, it is apparent that the infection of prawns with *A. cantonensis* occurred in recent times. It appears therefore that the surge of epidemics of the disease in the Pacific occurred because the islanders were unaware that their food, commonly eaten raw, had recently become contaminated by an introduced parasite in their environment.

Angiostrongyliasis is known to be found in areas where murine angiostrongylosis is endemic. The sources of infection include a variety of mollusks and paratenic hosts[9,11] that infect humans by being eaten raw or undercooked, being eaten accidentally with salad greens or ripe fruits, or eaten raw for supposed beneficial or curative qualities.

Some of the important varieties of hosts reported in the transmission of *A. cantonensis* to man include:

1. Mollusks: *Achatina fulica,* a land snail;[23,33] *Pila ampullacea,* an amphibious snail;[41] and *Cipangapaludina chinensis,* an aquatic snail.[21] Included are the land slugs *Laevicaulus alte*[29] and *Vaginalus plebeius.*[12]
2. Paratenic hosts: *Macrobrachium* sp., a freshwater prawn;[12] species of land planarians as suspected in New Caledonia;[7,17] species of frogs and toads, as reported in the Ryukyu;[40] and possibly certain species of amphibious[46] and land crabs.[8]

In addition to the above, the pelagic fish *Trachurops crumenophthalmus* (also referred to as "ature" and "akule") was found experimentally in 1967 to serve as carrier host for third-stage larvae of *A. cantonensis.*[50] In these experiments, even though the number of larvae recovered

from the fish was found greatly reduced within a few weeks after infection, some remained alive and infective for 29 days—the longest period tested. It was reported then that to incriminate this fish as a possible source of human infection, it is necessary to show the presence of the larval parasites in the fish in nature. This has not been confirmed to date. There is no record that marine fish in the Pacific are a source of angiostrongyliasis. In Hawaii raw fish ("sashimi"), derived from at least six types of marine fish including "akule", is eaten by many islanders, especially those of oriental ancestry. According to the Communicable Disease Division of the Hawaii State Department of Health, no case of eosinophilic meningitis (angiostrongyliasis) has yet been reported in Hawaii as transmitted by the eating of raw fish "sashimi" (personal communication, November 6, 1986). Although cases of angiostrongyliasis have been reported in Hawaii since 1961,[29,46] the source when known has been traced to the consumption of either raw snails[46] or slugs.[29] In one case, the mother of a 13-month-old-boy found a small snail in the child's mouth before the onset of the illness.[22]

Conclusion

Evidence indicates that eosinophilic meningitis first occurred in the Pacific Islands in the middle of this century, following the incoming of the giant African snail, *Achatina fulica,* believed responsible for the introduction of the rat lungworm, *Angiostrongylus cantonensis* in the area.

The first evidence of the relationship of the rat lungworm with eosinophilic meningitis was the concomitant finding of young adult *A. cantonensis* in the cerebrospinal fluid of a patient suffering with symptoms of meningitis in 1945.

In the wake of three epidemics of eosinophilic meningitis in the Pacific between 1948 to 1957, the rat lungworm was first theorized and later proven to be the etiological agent of eosinophilic meningitis, and this became recognized as a new parasitic disease of man referred to as "angiostrongyliasis cantonensis".

The source of human infection lies in the consumption of raw mollusks (snails and slugs), which serve as intermediate hosts of the parasite, or the consumption of raw paratenic (carrier) hosts harboring the infective third-stage larvae derived from feeding on infected mollusks. Such carrier or transport hosts thus far reported include naturally infected freshwater prawns, land planarians, species of frogs and toads, and possibly crabs.

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